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Comparing potential benefits of new pneumococcal vaccines with the current polysaccharide vaccine in the elderly

Alicia M. Fry [a,d], Elizabeth R. Zell [a,b], Anne Schuchat [a], Jay C. Butler [c], Cynthia G. Whitney [a,*]

[a] *Respiratory Diseases Branch, Center for Disease Control and Prevention, Mailstop C-23, 1600 Clifton Road, NE, Atlanta, GA 30333, USA*
[b] *Biostatistics and Information Management Branch, Center for Disease Control and Prevention, Mailstop C-23, 1600 Clifton Road, NE, Atlanta, GA 30333, USA*
[c] *Arctic Investigations Program, Center for Disease Control and Prevention, 4055 Tudor Centre Drive, Anchorage, AK 99508, USA*
[d] *National Center for Infectious Diseases, Epidemic Intelligence Service, Center for Disease Control and Prevention, Mailstop C-23, 1600 Clifton Road, NE, Atlanta, GA 30333, USA*

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Abstract

We compared the hypothetical effects of the 23-valent polysaccharide pneumococcal vaccine with new vaccines on preventing invasive and noninvasive pneumococcal disease in persons ≥65 years. We estimated how much disease would occur if no polysaccharide vaccine were in use and used this baseline to compare the polysaccharide, a 7-valent conjugate vaccine, and hypothetical common antigen vaccine. The polysaccharide, conjugate, and common antigen vaccines prevented 10.6, 10.7, and 17.7% of invasive disease and 4.3, 5.6, and 10.0% of pneumonia, respectively. Superior effectiveness of new vaccines was dependent upon a presumed longer duration of protection than the 23V-PPV and effectiveness against noninvasive pneumonia. Our results suggest that new vaccines could improve disease prevention.

Keywords: Pneumococcal vaccines; Potential benefits; Pneumonia

1. Background

In the United States, the 23-valent polysaccharide pneumococcal vaccine is recommended for all persons ≥65 years old and for persons 2–64 years of age with certain chronic illnesses [1]. Nearly half of the elderly population has received the polysaccharide vaccine; in 1997, 46% of persons ≥65 years of age reported that they were vaccinated [2]. Also, the vaccine's effectiveness against invasive pneumococcal disease has been documented [3,4]. Despite this, nearly 60,000 cases of invasive pneumococcal disease occur in the United States each year; one-third of cases and most deaths occur among the elderly [5].

Several new pneumococcal vaccines have been developed or are under investigation. A pneumococcal protein-polysaccharide conjugate vaccine, containing polysaccharides from the seven most common serotypes that cause invasive disease in children <5 years in the United States, has been approved for use in children (Prevnar®, Wyeth Lederle) [6]. Randomized clinical trials have demonstrated that the conjugate pneumococcal vaccine is protective against invasive disease, pneumonia, and otitis media in children <2 years [7–9]. Other formulations of conjugate vaccines, that contain 9 or 11 serotypes, are being evaluated. The effectiveness of conjugate vaccines has not been extensively studied for adults because of the existing polysaccharide vaccine, but also because of the limited number of serotypes included in the currently-licensed conjugate vaccine. The seven serotypes included in the 7-valent formulation cover 80% of invasive pneumococcal disease cases in children but only 56% of invasive cases in elderly persons [5]. Also, vaccines containing surface antigens common to all pneumococci-primarily proteins such as pneumococcal surface protein A, pneumococcal surface adhesin A, and pneumolysin-are in early stages of testing [10]. These vaccines, if effective, would protect against all pneumococci, regardless of serotype. If conjugate vaccines or common antigen vaccines are effective against noninvasive pneumococcal disease in adults, such as pneumonia without bacteremia, or if they induce immunologic memory and, therefore, confer longer protection, they may have advantages over the currently recommended polysaccharide vaccine [11].

We developed a model that compared the effect of the 23-valent pneumococcal polysaccharide vaccine with the

* Corresponding author. Tel.: +1-404-639-4737; fax: +1-404-639-3970.
E-mail address: cgw3@cdc.gov (C.G. Whitney).

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potential benefits of new vaccines on preventing pneumococcal disease in a cohort of the elderly, represented by the 1998 US population 65 years and older. First, we estimated the amount of disease that would occur if no polysaccharide vaccines were in use. We then used this baseline to compare the protective effects of the 23-valent pneumococcal polysaccharide vaccine with the theoretical effects of new pneumococcal vaccines against invasive pneumococcal disease, deaths due to invasive disease, and noninvasive pneumococcal pneumonia. We varied factors that are important in determining vaccine effectiveness to estimate the effect that these factors play on the overall protection afforded by the current polysaccharide vaccine and the potential protection that could be achieved if new vaccines improved upon any of these factors.

2. Methods

2.1. Step 1: Estimating the amount of pneumococcal disease if no vaccine were in use

2.1.1. Invasive pneumococcal disease

We determined age-group-specific incidence rates (cases per 100,000 population in 1998) of invasive pneumococcal disease for persons aged 65–74, 75–84 and ≥85 years from data collected by active bacterial core surveillance (ABCS) from 1 January to 31 December 1998, and assumed that rates were constant within age-groups. ABCS is an active, population-based system operating in nine Emerging Infectious Diseases program sites (total surveillance population of 17 million in 1998) [12]. ABCS methods are defined elsewhere [5,13]. ABCS defines a case of invasive pneumococcal disease as the isolation of *Streptococcus pneumoniae* from a normally sterile site. Rates of disease among the surveillance population and projected number of cases in the United States were calculated using US Bureau of the Census 1998 post-census population estimates [14]. For each age group, we estimated serotype-specific rates and projected cases by applying the proportion of total cases due to each serotype to the total rate or projected number of cases.

To estimate the rate of invasive pneumococcal disease that would have occurred if the 23-valent polysaccharide vaccine were not available—a hypothetical "no vaccine" baseline rate—we made assumptions about polysaccharide vaccine effectiveness, duration of protection, and vaccination levels and applied them to national projections for 1998 for cases caused by vaccine serotypes (Table 1). The number of invasive pneumococcal disease cases in the setting of no vaccine was estimated by dividing 1998 cases by (1 − (vaccine effectiveness × vaccination level)). The "no vaccine" incidence rates for each age group were calculated by summing the projected cases for each age group divided by the population. The percent decrease in cases was the 1998 ABCS invasive pneumococcal disease rate minus the "no vaccine" rate divided by the "no vaccine" rate.

We evaluated vaccine effect on the 1998 United States elderly population as a cohort. In the National Health Information Survey, 46% of elderly persons reported ever receiving the pneumococcal vaccine [2]. Data about age of vaccination in the elderly is not published; therefore, we assumed that 46% of the elderly cohort was vaccinated at 65 years of age. To account for persons who may have been vaccinated later, we assumed that an additional 8% of persons were vaccinated at age 75 years and 7% received vaccine at age 85 years [15].

Vaccine effectiveness for newly vaccinated 65-, 75-, and 85-year-old persons was estimated to be 75, 60, and 34%, respectively [4]. We assumed that the 23-valent polysaccharide vaccine was not protective against invasive disease in elderly persons with any immune-compromising condition, and that vaccine effectiveness against potentially cross-reactive serotypes was 60% of the vaccine-type effectiveness estimate [3]. Immune-compromised persons consisted of those with immunoglobulin deficiency, immunosuppressive therapy, leukemia, multiple myeloma, Hodgkin's disease, systemic lupus erythematosus, renal failure or dialysis, or nephrotic syndrome. The proportions of immune-compromised persons with invasive disease were 0.199, 0.173, and 0.142 for 65–74, 75–84, and ≥85-year-old persons, respectively [16]. Protection from the vaccine against invasive pneumococcal disease was assumed to decline gradually over time [4]. During the first 5 years after vaccination, we assumed maximum protection (100% of the initial vaccine effectiveness estimate), during years 5–9 after vaccination protection was 50% of the maximum estimate, and 10–14 years after vaccination protection was 25% of the maximum effectiveness estimate. The vaccines were assumed to be equally effective against all vaccine serotypes and to decline equally in protection.

We assessed the sensitivity of the final "no vaccine" disease rate estimates to base-case values by using high and low effectiveness estimates representing the 95% confidence limits of effectiveness estimates from published studies [3,4] (Table 1).

2.1.2. Deaths due to invasive pneumococcal disease

We determined age-group-specific mortality rate (deaths per 100,000 population in 1998) and the number of deaths due to invasive pneumococcal disease among persons ≥65 years in a "no vaccine" setting, with methods and assumptions the same as those described for cases of invasive pneumococcal disease (Table 1). Death due to invasive disease was defined as a case of invasive disease resulting in death before hospital discharge.

2.1.3. Noninvasive pneumococcal pneumonia

To estimate the number of persons ≥65 years hospitalized with pneumococcal pneumonia during 1998, we used ABCS data on invasive pneumococcal cases that had a diagnosis of pneumonia or in which *S. pneumoniae* was isolated from pleural fluid. Fifteen to thirty percent of pneumococcal

Table 1
Assumptions about the 23-valent pneumococcal polysaccharide vaccine and new pneumococcal vaccines used in base case and sensitivity analyses

Vaccines and assumptions	Base case	Sensitivity analysis[a]		Reference
		Low	High	
23-valent polysaccharide vaccine				
Maximum VE against IPD in healthy				
65-year-old	75%	47%	85%	[3,4]
75-year-old	60%			[3,4]
85-year-old	34%			[3,4]
VE against IPD, immune compromised persons	0%	–	–	[4]
VE against non-bacteremic pneumococcal pneumonia	0%	–	50%	[19,21,22]
Vaccination level, age of vaccination[b]				
65-year-old	46%		90%	[2,15]
75-year-old	8%			
85-year-old	7%			
Duration of maximum vaccine protection	5 years	–	–	
Percent of maximum VE by years since vaccination	1–5 years: 100% 6–10 years: 50% 11–15 years: 25% >15 years: 0%	–	–	[4,32]
Serotype coverage	85%			
New pneumococcal vaccines[c]				
VE against IPD in healthy elderly	75%	47%	85%	[20]
VE against IPD in immune-compromised persons	0%	–	–	–
VE against nonbacteremic pneumococcal pneumonia	50%	0%	73%	[8,20]
Vaccination level, age of vaccination 65-year-old	46%	–	90%	[2]
Duration of maximum protection	10 years	5 years	15 years	[4]
Percent of maximum VE by years since vaccination	1–10 years: 100% 11–20 years: 50% >20 years: 0%	1–5 years: 100% 6–10 years: 50% 11–15 years: 25% >15 years: 0%	1–15 years: 100% >15 years: 50%	–
Serotype coverage				
7V-pediatric conjugate	56%	–	–	[5,16]
11V-pediatric conjugate	65%			
Common antigen	100%			
7V-geriatric conjugate	60%			
11V-geriatric conjugate	72%			

VE: vaccine effectiveness, IPD: invasive pneumococcal disease, –: none.
[a] Base case estimates are used if no value is specified.
[b] For comparison among vaccines, assumed that no vaccine was given to older ages.
[c] 7V-pediatric conjugate, 11V-pediatric conjugate, common antigen, 7-geriatric conjugate, 11V-geriatric conjugate.

pneumonia in hospitalized elderly patients is bacteremic [17–19]. We assumed that 30% of all pneumococcal pneumonia cases in the elderly are bacteremic, an assumption that might underestimate the amount of non-invasive pneumococcal disease.

2.1.4. Step 2: Comparing the effect of different pneumococcal vaccines

We compared the effect of the polysaccharide vaccine on preventing pneumococcal disease with the theoretical effect of several new vaccines: a 7-valent conjugate vaccine (Prevnar®, Wyeth-Lederle) that includes serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F; an 11-valent conjugate formulation that includes those serotypes and 1, 3, 5, and 7F [11]; a hypothetical common antigen vaccine that protects against all serotypes; and two hypothetical geriatric 7-valent and 11-valent conjugate vaccines that contain the 7 and 11 most common serotypes that cause invasive disease in the US elderly, serotypes 3, 4, 6B, 9V, 14, 22F, 23F, and those plus 11A, 12F, 18C, and 19F, respectively [16]. We also compared strategies that combined the polysaccharide vaccine and 7-valent pediatric conjugate vaccine. One included administering the polysaccharide vaccine and 7-valent conjugate vaccine in the same year, appropriately spaced so that the effectiveness of neither vaccine was compromised. The second strategy was giving the 23-valent polysaccharide vaccine at age 65 years and the 7-valent conjugate vaccine 5 years later, a scenario that would occur if the 7-valent conjugate vaccine were recommended for elderly persons already vaccinated. We did not assume that the two vaccines had

negative or positive synergistic effects on the effectiveness of each other.

2.1.5. Invasive pneumococcal disease

We estimated the effect of each pneumococcal vaccine on reducing invasive pneumococcal disease cases from the "no vaccine" baseline rate. We made base-case, low and high estimates for vaccine efficacy, duration of protection, and vaccination level (Table 1). In contrast to Step 1, we assumed that vaccination occurred only at age 65 years. All vaccine assumptions were applied to the "no vaccine" serotype-specific rates for each age-group. Vaccine-modified rates were calculated by multiplying the "no vaccine" rate by (1 − (vaccine effectiveness × vaccination level)). The percent decrease in cases was the vaccine-modified rate minus the "no vaccine" rate divided by the "no vaccine" rate.

For the polysaccharide vaccine, we used the same assumptions about vaccine effectiveness and duration of protection as described in Step 1 (Table 1). For the new vaccines, we do not have clinical studies on which to base our assumptions. There is limited data that demonstrated comparable antibody responses for the polysaccharide and conjugate vaccines in adults [20], therefore, for our base-case assumption, we assumed equal effectiveness against invasive disease as the polysaccharide vaccine, but we included lower and higher estimates of effectiveness in our sensitivity analysis. Because duration of protection may be one area where new vaccines could improve upon the current vaccine, we assumed that a conjugate vaccine would have a longer duration of protection than a polysaccharide vaccine because of T cell dependent immune response-induced memory. Vaccine effectiveness for potentially cross-reactive vaccine serotypes of the conjugate vaccines was assumed to be 75% of maximum effectiveness [9]. No data is available to aid in the assumptions for a hypothetical common antigen vaccine, therefore, we made similar assumptions for the common antigen vaccine as the conjugate vaccine, only serotype coverage was different. To compensate for the assumptions that were not based on scientific evidence, we included a sensitivity analysis with low and high estimates for each factor that affects the overall protection that each vaccine provides.

2.1.6. Deaths due to invasive pneumococcal disease

We determined the number of deaths prevented by vaccination and percent decrease with methods and assumptions that were the same as those described for cases of invasive disease (Table 1).

2.1.7. Hospitalized noninvasive pneumonia

The effectiveness of the polysaccharide vaccine against non-invasive pneumococcal disease has not been established. Three randomized controlled trials failed to demonstrate efficacy of the 23-valent polysaccharide vaccine against non-bacteremic pneumococcal or non-specific pneumonia in the elderly [19,21,22]. One retrospective cohort study suggested that vaccine effectiveness may be 50% against pneumococcal pneumonia among elderly persons with chronic lung disease [23]. In a controlled trial in children, the 7-valent conjugate vaccine had an efficacy of 73% against "all cause bacterial" pneumonia, defined as consolidation >2.5 cm on chest X-ray [8]. We assumed that base case vaccine effectiveness against pneumococcal pneumonia for the polysaccharide vaccine was 0% in the elderly, but included sensitivity estimates that reflect current data for the polysaccharide vaccine (Table 1). For the new pneumococcal vaccines, we assumed that base case vaccine effectiveness against vaccine serotype-specific pneumococcal pneumonia was 50% in the elderly, but included high and low sensitivity estimates that reflect potential values for the new vaccines.

We calculated the number of cases of noninvasive pneumococcal pneumonia prevented by each vaccine by multiplying the age-group-specific number of cases in immune competent individuals by ((vaccine effectiveness) × (vaccination level) × (serotype coverage)). The percent decrease in cases was the vaccine-modified cases minus the estimated number of pneumonia cases in 1998 divided by total 1998 cases.

3. Results

3.1. Disease burden without polysaccharide vaccine

The age- and race-adjusted rate of invasive pneumococcal disease among persons ≥65 years old in 1998 was 59.8 cases per 100,000 population, or approximately 20,540 cases per year in the United States (Table 2). The rate of invasive disease if no vaccine were used, i.e. the estimated "no vaccine" rate, was 68.2 cases per 100,000 or 23,480 cases per year. Therefore, use of the polysaccharide vaccine among persons ≥65 years prevented 2800 cases of invasive pneumococcal disease in 1998, a 12.4% decrease compared to a setting with no vaccine. The "no vaccine" rate was 67.0 cases per 100,000 (10.6% decrease in invasive disease) if we did not include vaccination at 75 and 85 years of age. Most of the prevented cases occurred in the 65–69-year age group, the group that received the vaccine within the previous 5 years (Table 2). The rates of invasive disease with no vaccine were 64.5/100,000 and 69.9/100,000 if the low and high vaccine effectiveness assumption values were used (7.3 and 14.4% decrease in cases, respectively).

The age- and race-adjusted mortality rate due to invasive pneumococcal disease in persons ≥65 years old in 1998 was 9.9 deaths per 100,000, or approximately 3400 deaths per year. The rate if no vaccine was used, the estimated "no vaccine" mortality rate, was 11.2 deaths per 100,000 or 3,870 deaths per year. Therefore, use of the polysaccharide vaccine in 1998 prevented 460 deaths due to invasive pneumococcal disease among elderly persons, a 12.0% decrease. Given the base estimate of zero efficacy, the polysaccharide vaccine prevented none of the approximately 30,000 cases of

Table 2
Estimation of the number of cases of invasive pneumococcal disease in person's ≥65 years of age in 1998 if there were no pneumococcal vaccine, an estimation of the effect of the 23-valent polysaccharide pneumococcal vaccine

Age group (years)	1998 with vaccine			Hypothetical "no vaccine"			Decrease due to vaccine[a] (%)
	Immune-compromised	Others	Total	Immune-compromised	Others	Total	
65–69	802	3225	4027	802	4774	5576	27.8
70–74	736	2959	3695	736	3534	4270	13.5
75–79	851	4064	4915	851	4673	5524	11.0
80–84	557	2668	3225	557	2724	3281	1.7
≥85	666	4016	4682	666	4195	4861	3.4
Total			20540			23480	11.8

[a] Decrease $= \frac{\text{number of cases in 1998} - \text{mumber of cases without vaccine}}{\text{number of cases without vaccine}} \times 100.$

hospitalized non-invasive pneumococcal pneumonia among US elderly persons in 1998.

3.2. Comparing the effect of pneumococcal vaccines

3.2.1. Analysis with base case estimates

Starting from the "no vaccine" baseline, use of either the polysaccharide vaccine or 7-valent conjugate vaccine resulted in a similar decrease in number of invasive pneumococcal disease cases among the elderly (10.6% versus 10.7%, respectively) (Table 3). More cases were prevented with use of an 11-valent conjugate vaccine (12.7%) or a hypothetical common antigen vaccine (17.7%). Hypothetical geriatric-formulated conjugate vaccines offered little additional protection compared with pediatric-formulated vaccines (7-valent geriatric conjugate 11.4%, 11-valent geriatric conjugate 14.4%) (Fig. 1). Combinations of the polysaccharide vaccine and 7-valent pediatric conjugate vaccine prevented more cases of invasive pneumococcal disease than either of these two vaccines alone. Giving the polysaccharide vaccine at age 65 followed by the 7-valent conjugate vaccine 5 years later provided the most protection against invasive pneumococcal disease in this model (19.0% decrease); giving polysaccharide vaccine and 7-valent conjugate vaccine in the same year resulted in a 14.2% decrease (Fig. 1). Conversely, if the 7-valent pediatric vaccine was given at 65 years of aged followed by the polysaccharide vaccine at age 70 years, 14% of invasive pneumococcal disease would be prevented.

The effect of the vaccines on deaths due to invasive pneumococcal disease closely resembled the effect on invasive disease cases (Table 3). The 23-valent pneumococcal polysaccharide vaccine prevented a similar number of deaths as the 7-valent pediatric conjugate vaccine (10.2% (394 deaths) versus 10.1% (390 deaths), respectively). The 11-valent conjugate vaccine would prevent 464 (12.1%) deaths due to invasive pneumococcal disease, and a common antigen vaccine, 647 deaths (16.7%).

If new pneumococcal vaccines were effective against vaccine serotype specific pneumonia, we estimated that a

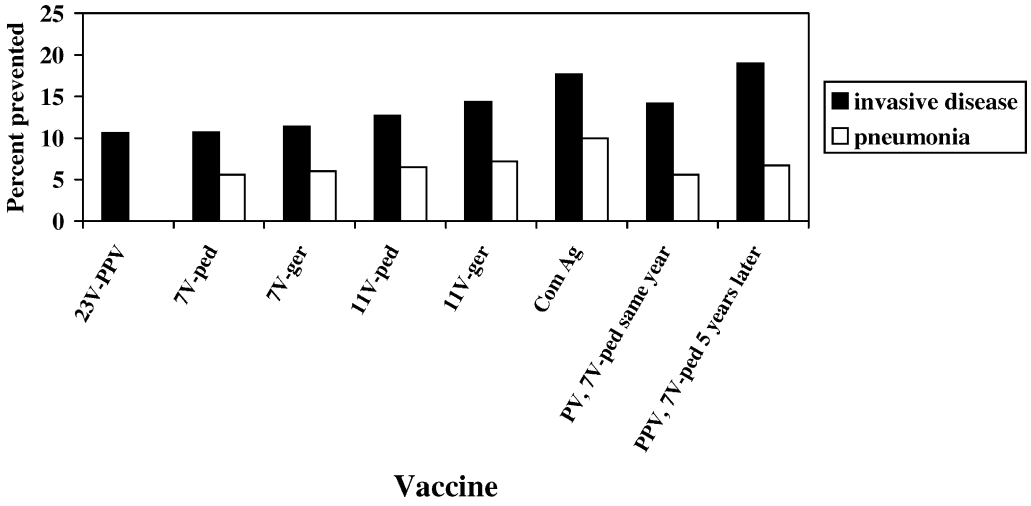

Fig. 1. Comparison of different vaccine formulations and strategies for reducing cases of invasive pneumococcal disease and hospitalized noninvasive pneumococcal pneumonia, using base-case assumptions (23V-PPV = 23-valent polysaccharide vaccine, 7V-ped = 7-valent pediatric conjugate vaccine, 7V-ger = 7-valent geriatric conjugate vaccine, 11V-ped = 11-valent pediatric conjugate vaccine, 11V-ger = 11-valent geriatric conjugate vaccine, Com Ag: common antigen vaccine).

Table 3
Sensitivity analysis for comparison of pneumococcal vaccines: percent decrease in (A) invasive pneumococcal disease cases, (B) deaths due to invasive disease, and (C) hospitalized noninvasive pneumococcal pneumonia

Variable	Base	Sensitivity analysis[a]	
		Low	High
(A) Percent decrease in IPD cases			
Vaccine effectiveness			
23V-polysaccharide	10.6	6.7	12.0
7V-conjugate pediatric	10.7	6.7	12.1
11V-conjugate pediatric	12.7	8.0	14.4
Common antigen	17.7	11.1	20.1
Vaccination level			
23V-polysaccharide	10.6	–	20.8
7V-conjugate pediatric	10.7	–	20.9
11V-conjugate pediatric	12.7	–	24.8
Common antigen	17.7	–	34.6
Duration of maximum protection			
23V-polysaccharide	10.6	–	–
7V-conjugate pediatric	10.7	6.7	15.0
11V-conjugate pediatric	12.7	8.1	17.4
Common antigen	17.7	11.4	24.2
(B) Percent decrease in deaths due to IPD			
Vaccine effectiveness			
23V-polysaccharide	10.2	6.4	11.5
7V-conjugate pediatric	10.1	6.3	11.4
11V-conjugate pediatric	12.1	7.5	13.5
Common antigen	16.7	10.5	18.9
(C) Percent decrease in non-invasive pneumococcal pneumonia			
Vaccine effectiveness			
23V-polysaccharide	0	–	4.9
7V-conjugate pediatric	5.6	0	8.2
11V-conjugate pediatric	6.5	0	9.5
Common antigen	10.0	0	14.7
Vaccination level			
23V-polysaccharide	0	–	9.6
7V-conjugate pediatric	5.6	–	11.0
11V-conjugate pediatric	6.5	–	12.7
Common antigen	10.0	–	20.0
Duration of maximum protection			
23V-polysaccharide	0	–	–
7V-conjugate pediatric	5.6	3.2	8.4
11V-conjugate pediatric	6.5	3.8	9.7
Common antigen	10.0	7.7	15.7

[a] Assuming all other variables are base-case values, IPD: invasive pneumococcal disease, V: valent.

7-valent pediatric conjugate vaccine would prevent 1660 cases (5.6% decrease), an 11-valent conjugate vaccine 1930 cases (6.5% decrease), and common antigen vaccine 2970 cases (10.0% decrease) (Table 3).

3.2.2. Sensitivity analysis

The differences in the amount of invasive pneumococcal disease, deaths due to invasive disease, and noninvasive pneumococcal pneumonia that were prevented were small when the low and high vaccine effectiveness assumption values were used for each vaccine (Table 3). Alterations in vaccine coverage estimates directly correlated with the amount of invasive pneumococcal disease and pneumonia that each vaccine could prevent; doubling vaccine coverage to 90%, the Healthy People 2010 goal [23], resulted in a two-fold increase in the amount of invasive pneumococcal disease and noninvasive pneumococcal pneumonia prevented by each vaccine (Fig. 2). Duration of vaccine protection was also very important in the amount of disease that a vaccine could prevent. If the protection provided by the new vaccines was similar to the polysaccharide vaccine, that is it began to decline after 5 years (with waning protection over 15 years), the new vaccines would offer less or only slightly better protection against disease than the current vaccine (Table 3). In this scenario, a common antigen vaccine would prevent similar amounts of disease (11.4%) as the current polysaccharide vaccine (10.6%). However, if protection did not begin to decline until after 15 years (with waning protection over 25 years), the new vaccines would prevent a substantially larger amount of invasive disease and noninvasive pneumococcal pneumonia in the elderly.

If we assumed high values for vaccine effectiveness, duration of protection, and coverage, a best-case scenario, all of the new vaccines, or strategies that combine the polysaccharide vaccine with a 7-valent pediatric conjugate vaccine, would prevent more cases of invasive disease, deaths due to invasive disease, and noninvasive pneumococcal pneumonia than the best case scenario of the polysaccharide vaccine. If a hypothetical common antigen vaccine was 85% effective against invasive disease and 73% against pneumonia, protection was optimal for 15 years (waning over 25 years), and 90% of elderly persons received the vaccine, the vaccine would prevent 12,580 cases of invasive disease (53.6% decrease), 2033 deaths (52.6% decrease) and 12,698 cases of non-invasive pneumonia (42.8% decrease). Under the same conditions the 7-valent pediatric conjugate vaccine would prevent 7792 cases of invasive pneumococcal disease (33.2%) and 7110 cases of non-invasive pneumonia (23.9%). If the 23-valent pneumococcal polysaccharide vaccine had 85% vaccine effectiveness against invasive disease and 50% against pneumonia, protection began to decline after 5 years (waning protection for 15 years), and 90% of elderly were vaccinated, 5513 cases (23.5%) of invasive pneumococcal disease and 3364 cases of non-invasive pneumonia (11.3%) would be prevented.

4. Discussion

We estimated that use of the polysaccharide vaccine among elderly persons prevented about 3000 cases of invasive pneumococcal disease in 1998, 12.4% less than would occur if no vaccine were available. Most cases were prevented in the first 5 years after vaccination, when the vaccine was maximally effective. Similarly, use of the polysaccharide vaccine in 1998 prevented 12.0% of deaths due to invasive disease in this population. Doubling current

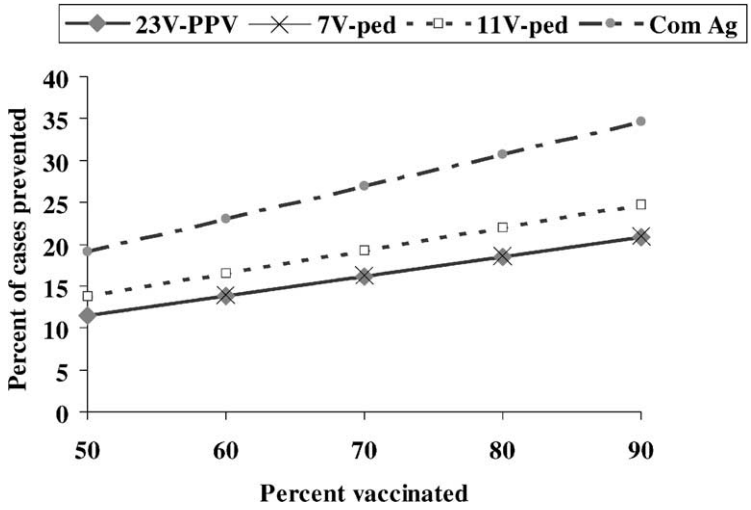

Fig. 2. Comparison of different pneumococcal vaccines on the effect on invasive pneumococcal disease cases, by vaccination level (23V-PPV = 23-valent polysaccharide vaccine, 7V-ped = 7-valent pediatric conjugate vaccine, 11V-ped = 11-valent pediatric conjugate vaccine, Com Ag: common antigen vaccine).

vaccination levels to meet the Healthy People 2010 goal of 90% could prevent twice as many invasive pneumococcal disease cases among elderly persons [24].

The duration of vaccine protection against disease was a limitation of the polysaccharide vaccine and an area where new vaccines might offer advantages over the current vaccine. If 7- and 11-valent conjugate vaccines offered protection against invasive pneumococcal disease for at least 10 years, they may be as effective as the current vaccine at reducing pneumococcal disease in the elderly, despite coverage against fewer serotypes. Hypothetical common antigen vaccines, if they are effective in elderly persons, offer the greatest potential to significantly decrease cases of pneumococcal disease. Because booster doses can be given for conjugate and protein vaccines, the duration of protection for these new vaccines could, theoretically, be extended to values close to our high sensitivity estimates. If new pneumococcal vaccines are to be considered for adults, studies that assess the duration of protection would be important.

The low proportion of cases that we estimated to be prevented by the 23-valent pneumococcal polysaccharide vaccine was surprising. Improving vaccine coverage, however, would improve the number of cases prevented. Also, 14–20% of pneumococcal disease occurs in persons with immune-compromising conditions [16]; if vaccines are effective in some immunocompromised persons, the number of cases prevented may be higher than we estimated. Finally, we assumed that most people were vaccinated at 65 years of age, according to current recommendations. Since the risk of pneumococcal disease increases with advancing age and vaccine effectiveness wanes over time, many cases of pneumococcal disease are not prevented in later years [4]. Current recommendations do not suggest routine revaccination for individuals >65 years [1]. In studies that compared the immune response of revaccination to first time recipients, the immune response was inferior after revaccination in all studies [25–29] but one [30]. Clearly, more research is needed to determine the effectiveness of revaccination with the polysaccharide vaccine.

Although our estimates of the number of cases of hospitalized non-invasive pneumococcal pneumonia in the elderly are crude, it is clear that non-invasive pneumococcal pneumonia causes the majority of disease due to *S. pneumoniae* in the elderly. An optimal pneumococcal vaccine strategy for the elderly is one with demonstrated effectiveness against non-invasive pneumococcal pneumonia. Studies to determine the effectiveness of the current and new pneumococcal vaccines against pneumonia in healthy elderly persons are needed.

There are some limitations to our analysis. First, our model was unable to incorporate some factors that may influence vaccine effect in the elderly, such as the effect of conjugate and common antigen vaccines on pneumococcal transmission and disease if nasopharyngeal carriage is decreased. If such herd immunity occurs, new vaccines could have an effect larger than we estimated. Also, the serotypes in the pediatric vaccines are more likely to have drug resistance [13]; if conjugate vaccines had better efficacy against these serotypes than the current vaccine they could effect the amount of disease due to drug-resistant pneumococci. Next, data regarding vaccination levels are collected from surveys dependent upon patient recall, which is potentially insensitive among elderly persons. In addition, we have limited information regarding age of vaccination in the elderly; if we are correct about our estimate of level of vaccination, but vaccination was distributed throughout age groups, we expect little difference in the number of cases prevented. Finally, we have little or no data regarding conjugate or

common antigen vaccine performance in adults. To compensate for this, we included a sensitivity analysis with high and low estimates that cover a range from zero to optimal values.

Studies have compared anti-polysaccharide antibody concentration after vaccination of adults with conjugate vaccines and polysaccharide vaccine and have found them to be similar [20,31]. However, the optimal dose, number of doses, or dosing interval of conjugate vaccine for adults has not been determined and anti-polysaccharide antibody concentration have not been correlated with vaccine protection. Antibody concentration weeks or months after immunization may fail to account for the variety of protective immune responses that might be achievable with a protein-polysaccharide conjugate or protein antigen compared to a polysaccharide antigen and do not provide a measure of immune memory established by T cell dependent antigens. Therefore, our assumption of equal effectiveness among all the vaccines but longer duration of protection for the conjugate and common antigen vaccines was an acceptable option.

Our analysis clearly indicates that pursuing research on the performance of new vaccines in adults is critical. Our model has provided a glimpse of what might be possible if new vaccines had good efficacy and duration of protection in elderly adults, and has identified key areas of uncertainly regarding the effects that are possible with use of the polysaccharide vaccine, including the duration of protection for different age groups, the effectiveness of revaccination, and the effectiveness against pneumonia. Clinical studies are the next step in determining the value of new pneumococcal vaccines for adults. Assessing duration of protection and the induction of immunologic memory should be key components of research on new pneumococcal vaccines for adults. In the meantime, many persons who could benefit from the polysaccharide vaccine have not yet received it. Promoting use of the currently available pneumococcal vaccine could prevent thousands of cases and hundreds of deaths while research on newer vaccines continues.

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